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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/746,567 | 12/21/2000 | Angel Cebolla Ramirez | AM-00106.P.1-US | 1592 |

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| EXAMINER | |
|---|---|
| PAPPU, SITA S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | 7 |

DATE MAILED: 07/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/746,567 | CEBOLLA RAMIREZ ET AL. | |
| | Examiner | Art Unit | |
| | Sita S Pappu | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17-47* is/are pending in the application.

4a) Of the above claim(s) *42 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,17 and 43-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Claims 17-47 are pending in the instant application. This office action is in response to the communication filed by the Applicant on 06/03/2002 (paper #6).

### *Election/Restrictions*

Applicant's election, without traverse, of Group I, claims 17-41, 43-46 is acknowledged. Accordingly, claims 42 and 47 are withdrawn from consideration as being directed to non-elected subject matter. This paper contains an examination of claims 17-41, 43-46 on their merits.

### *Priority*

Applicant's claim of priority to the PCT application PCT/IB00/00830 filed 06/22/2000, and the foreign applications ES-200001389 filed 05/31/2000 and ES-9901383 filed 06/22/1999 is acknowledged.

It is noted, however, that applicant has not filed a certified copy of the foreign applications ES-200001389 and ES-9901383, as required by 35 U.S.C. 119(b).

### *Oath/Declaration*

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application, by application number and filing date, is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because the title of the invention is incorrect.

The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or

declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

***Drawings***

Draftsperson objected to the drawings. See PTO-948 attached to paper #5, mailed 04/23/2002. Applicant is required to submit the drawing corrections within the time period set in this Office Action. See 37 C.F.R. 1.85(a). Failure to take corrective action within the set time period will result in ABANDONMENT OF THE APPLICATION.

***Specification***

The disclosure is objected to because of the following informalities:

Specification, on page 1, under "related applications" refers to Spanish Application ES-200001389 filed in the name of "Ramierz et al" where the name of the inventor is misspelled.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-41, 43-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cascade genetic circuit comprising a plurality of transcriptional regulators wherein expression of an upstream transcriptional regulator stimulates expression of at least one downstream transcriptional regulator,

which in turn stimulates a target promoter, wherein the cascade genetic circuit is provided in vitro, and a method of regulating the expression of a nucleic acid molecule in vitro in gram negative bacteria or in eukaryotic cells for magnification of gene expression wherein the cascade is inducible by a salicylate molecule and leads to overproduction of polypeptides in vitro and in cell cultures, does not reasonably provide enablement for the use of the cascade genetic circuit in vivo in methods of gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention and Breadth of claims:

Claims 17-41, 43-46 are directed to a cascade genetic circuit comprising a plurality of transcriptional regulators, wherein expression of an upstream transcriptional regulator stimulates expression of at least one downstream transcriptional regulator,

which in turn stimulates a target promoter, wherein the cascade genetic circuit is provided in vitro, or in vivo and a method of regulating the expression of a nucleic acid molecule in gram negative bacteria or in eukaryotic cells for magnification of gene expression wherein the cascade is inducible by a salicylate molecule, thereby overproducing a variety of molecules under the control of the target promoter which include hormones, enzymes, growth factors, apolipoprotein, therapeutic proteins, diagnostic molecules, diagnostic proteins, antisense molecules, ribozymes, rRNA, tRNA,snRNA and portions or derivatives thereof, and a method of regulating expression of all these molecules using the cascade genetic circuit of the instant invention.

The claims encompass the use of the cascade genetic circuit and the method of regulating gene expression for gene therapy purposes in any eukaryotic cell and any mammalian cell. The claims encompass the use of the instant invention in human beings for gene therapy and are very broad.

Amount of Direction provided and existence of working examples:

The prior art teaches a method of transfecting cells and expressing exogenous nucleic acids in cells through cascade genetic systems. However, prior art does not teach expression of exogenous nucleic acids for the purpose of gene therapy in cells of whole organisms to such levels that a therapeutic effect is obtained. In cases where prior art does not teach how to use the method, all the guidance for practicing the invention must come from the specification. The specification fails to disclose the expression of any therapeutic gene in any art accepted animal model or patient, and nor does it provide guidance on how long the enhanced expression of exogenous nucleic

acids in the cells of organisms lasts, and whether it is long enough to see a therapeutic effect.

Examples 1 (page 10) and 2 (page 15) of the specification describe the use of the cascade genetic circuit for overexpression of lacZ (example 1) and a membrane protein (example 2). Example 3 (page 16) teaches the induction of the system with different salicylate derivatives using β-galactosidase as the reporter and disclose that the effector molecules NahR and XylS2 can synergistically amplify gene expression and show more gene expression capacity than the simple circuits (page 16, bottom paragraph and Table 3). Example 4 (page 18) teches that the efficiency of this genetic circuit depnds on the correct hierarchy of the regulators where xylS2 /Pm is downstream of the nahR/Psal in the circuit. Example 5 (page 19) discloses that the cascade system can be redesigned for use in organisms other than E. coli, such as Pseudomonas putida and that forms of xylS, other than xylS2, can exhibit this amplification property.

The specification, however, fails to provide any guidance on the effectiveness of the cascade system and the method of gene regulation for therapeutic purposes using any gene of therapeutic interest and fails to provide guidance on therapeutic parameters such as the dosages, routes of administration, frequency of administration. The specification further does not disclose for how long the amplification effect was observed, and whether repeat applications were necessary and if so, how frequently they were needed, and the level of gene expression needed to achieve this result, such that one of skill in the art would accept that their method would result in a therapeutic

outcome and be able to practice the method using the guidance provided in the specification.

Without specific guidance, it is not predictable that the results obtained in vitro correlate to results expected in vivo such that one of skill would have reasonable expectation of obtaining therapeutic levels of expression of any gene of interest. It is unpredictable how long the enhanced expression of the gene of interest due to the cascade mode of expression would last such that a therapeutic effect is seen using the method of the instant invention. It would require undue experimentation on the part of a skilled artisan to determine the vector, the dosage, frequency and route of administration, to obtain a level of expression that would result in a therapeutic effect.

Further, claims 40, 41, 43, 45, 46 are directed to a method for regulating the expression of a nucleic acid molecule, a method for making a moiety but fail to recite the expression of the constructs to produce the encoded product in any cells. As such the claims encompass any in vitro method of expressing the protein or molecule encoded by the construct, including in vitro translation. In such a situation, it would be unpredictable how an in vitro method, for example, an in vitro translation method, can regulate the expression of a nucleic acid molecule, and how the produced protein or molecule can have any therapeutic effect and thus, would require undue experimentation on the part of a skilled artisan to achieve any therapeutic result using the method of claims 40, 41, 43, 45, 46.

State of the art:

At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or plasmid DNA/liposome complexes, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2).

Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, particularly against adenoviral proteins, and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that

only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Predictability of the Art, Amount of Experimentation and Skill level of the artisan:

While it is relatively routine in the gene transfer art to achieve expression at non therapeutic levels, i.e., expression at low levels or at levels providing no patentably useful phenotypic effect, it is unpredictable without specific guidance and direction whether one will definitively achieve expression of a particular molecule at levels sufficient for a therapeutic effect. Thus, when there is deficiency in the art in terms of predictability of obtaining therapeutic levels of expression, the Applicant must provide sufficient guidance and direction which demonstrates or reasonably correlates to therapeutic levels of expression of a DNA product in an art recognized animal model or patient as claimed.

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the

invention as specified and use the invention as claimed over the full scope. The specification and the working examples do not provide sufficient guidance to practice the invention as claimed over the full scope. Therefore, in the absence of specific guidance and working examples, the use of the claimed cascade mode of expression in vivo for therapeutic purposes or in gene therapy is unpredictable. In such a situation, one skilled in the art would not know how to use the invention as claimed, without undue experimentation. In view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to use the invention.

Thus, due to the art recognized unpredictability of achieving therapeutic levels of gene expression following direct or indirect administration of nucleic acids, the lack of guidance provided by the specification for the parameters affecting delivery and expression of therapeutic amounts of DNA into the cells using the cascade system of the instant invention, the lack of guidance concerning the treatment of any disease using the claimed method of the instant invention, it would have required undue experimentation to practice the instant invention and the skilled artisan would not have predicted success in using the claimed method for therapeutic purposes. Thus the specification does not enable one skilled in the art to use the claimed invention in gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 40, 41, 43-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is indefinite in its recitation of "comprises a polypeptide". It is not clear how a nucleic acid molecule can comprise a polypeptide. Use of claim language such as "comprises a nucleic acid sequence encoding a polypeptide" is suggested.

Claims 40, 41, 43, 45, 46 are indefinite because the claims do not recite any cells for the use of the methods. The claims are directed to a method for regulating the expression of a nucleic acid molecule, a method for making a moiety but fail to recite any cells for the expression of the constructs to produce the encoded product. As such the claims encompass any in vitro method of expressing the protein or molecule encoded by the construct, including in vitro translation. In such a situation, it is not clear how an in vitro translation method can regulate the expression of a nucleic acid molecule. Clarification is required. Claim 44 is rejected insofar as it depends from claim 43.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308 4242 for regular communications and (703) 872 9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
June 28, 2002